PATENT SPECIFICATION

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(21) Application No. 10003/77 (22) Filed 9 March 1977
(31) Convention Application No. 7603157
(32) Filed 10 March 1976 in
(33) Sweden (SE)
(44) Complete Specification published 17 May 1978
(51) INT CL² A61K 47/00
(52) Index at acceptance
A5B 753 75Y 764

(19)

(54) MANUFACTURE DOSAGE UNITS

(71) We, ACO LAKEMEDEL AB, a Swedish Body Corporate of S—171,03, Solna, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new method for the manufacture of dosage units and is particularly concerned with the combined manufacture and packing of pharmaceutical dosage units in tablet form.

For conventional tablet manufacture, the internationally established rules known as GMP (Good Manufacturing Practice) require substantial investment in machinery and appliances, primarily to eliminate cross-contamination and spreading of dust.

The present invention provides a method for the production of dosage units in solid form which comprises mixing at least one biologically active material with a carrier which is solid at 20°C but liquid when heated to a temperature above 20°C, transferring portions of the melted carrier containing active material into pre-moulded cavities in a flow-line comprising at least one strip of a metal or a natural or synthetic plastic material and then sealing the filled cavities with a cover foil.

According to the invention, dosage units can be produced in tablet form with a fully guaranteed homogenous structure, each particle of the active substance being wholly covered by a carrier substance which, if desired, may be used in large quantities (up to nearly 100%) without complicating industrial scale manufacture. The method permits a finish equal to that of conventional sugar-coated tablets. The method is designed primarily for pharmaceutical substances in tablet form but is applicable to any biologically active material which it is desired to present in dosage units.

A conventional technique for tablet manufacture comprises several steps as enumerated in the table below. The various steps of the new method are listed adjacently.

Conventional tablet manufacture and packing	New method according to the invention
1. Active pharmaceutical substances is mixed with powdered excipient	1. Active pharmaceutical substance is added to melted carrier material
2. Powder mixture is granulated, dry or with additives	2. The melted composition is dispensed into the final individual packing
3. Powder mixture is dried and screened	
4. Lubricant is added	
5. Mixture is compressed in tablet machine	
6. Coating	
7. Finished tablets are packed	

The present invention involves introducing the active component, consisting of one or perhaps several active compounds, into a liquid carrier that is solid at 20°C e.g. room temperature, portions of this mixture are then transferred into the cavities in the flow-line made of plastic e.g. cellulose or metal in the form of a single strip or a laminate of more than one of the materials. The flow-line which also serves as a packing for the active substance is moulded with cavities corresponding to the desired form of the final dosage units.

The carrier may be a fat, fat mixture, other lipid substance or lipid component. Instead of, or in combination with, lipid substances or lipid-type substances, the carrier may contain other substances such as, waxes or thermoplastics, or water-soluble material of the polyethylene-glycol type. Examples of suitable thermoplastic materials include polyvinyl chloride, polyethylene, polypropylene, polyamides, polystyrene and polyvinylidene chloride. Other organic substances may be used, such as carbamides or paraffins. The

fats which may be used as carrier can be hardened vegetable fats such as hardened rapeseed oil. Other lipid substances or lipid components which can be used are stearic acid, palmitic acid, cetyl alcohol, cetyl acetate or stearyl alcohol. All carrier substances must be pharmaceutically acceptable products if the active compound is to be used as a pharmaceutical.

The carrier preferably has a melting point above 37°C, and particularly above 43°C.

One of the many advantages of the invention is the fact that it may be carried out practically independently of the quantitative proportions of active component and carrier substance which means that, regardless of such technical difficulties as may arise in production according to the methods previously known, the active component may be incorporated in the exact concentration desired in each special case. One large single dose with sustained release is often desirable as it facilitates medication. For this, the carrier and active pharmaceutical component are blended in the desired proportions of the finished dosage unit. According to the invention, the size of the dosage units may be predetermined without the use of drop-measuring devices, and without having any of the disadvantages connected with conventional granulate and tablet production.

In other cases, very small amounts of the drug are required. With the conventional methods, this causes serious problems with regard to mixing. Such problems are easily overcome with the method according to the invention as the mixing takes place in the liquid state.

In the aforementioned mixing stage, the active component should be used in finely powdered form, for instance, with an average grain size of 15 to 100μ, preferably 20 to 50μ, or in micro crystalline form. It may also be suspended or emulsified in a liquid to be worked into the carrier substance.

It is also possible to incorporate inert filling material in the mixture.

On an industrial scale, a flow-line can be obtained from a suitable thermoplastic wrapping sheet which is vacuum moulded with cavities corresponding to the dosage unit volume. Into these cavities the melted mixture consisting of carrier with incorporated active component is poured either with or without a measuring device. Any excess is removed, the flow-line is cooled or allowed to cool by itself, and the finished packing containing the dosage unit is sealed with a cover foil.

WHAT WE CLAIM IS:—

1. A method for the production of dosage units in solid form which comprises mixing at least one biologically active material with a carrier which is solid at 20°C but liquid when heated to a temperature above 20°C, transferring portions of the melted carrier containing active material into pre-moulded cavities in a flow-line comprising at least one strip of a metal or a natural or synthetic plastic material and then sealing the filled cavities with a cover foil.

2. A method according to claim 1 wherein the carrier has a melting point above 37°C.

3. A method according to claim 2 wherein the carrier has a melting point above 43°C.

4. A method according to any one of the preceding claims wherein the active material having an average grain size of 15 to 100 microns, is incorporated in the molten carrier and portions then introduced into the cavities.

5. A method according to any one of the preceding claims wherein the active material is a pharmaceutical.

6. A method according to claim 1 substantially as hereinbefore described.

7. A dosage unit obtained by a method according to any one of the preceding claims.

J. A. KEMP & CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn,
London, WC1R 5EU.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1978
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.